

CLAIMS

What is claimed is:

1. An isolated complex comprising a TGF-beta binding protein and a BMP antagonist protein in specific association, wherein:

(i) the TGF-beta binding protein comprises a sclerostin polypeptide that is capable of specifically binding a first TGF-beta superfamily member polypeptide that is selected from the group consisting of a BMP-5 polypeptide and a BMP-6 polypeptide, and

(ii) the BMP antagonist protein is selected from the group consisting of a Chordin polypeptide and a Noggin polypeptide, said BMP antagonist protein being capable of specifically binding at least one second TGF-beta superfamily member polypeptide that is selected from the group consisting of a BMP-2 polypeptide, a BMP-4 polypeptide and a BMP-7 polypeptide,

and wherein the complex is incapable of binding to the first TGF-beta superfamily member polypeptide.

2. An isolated complex comprising a first and a second TGF-beta binding protein in specific association, wherein;

(a) the first TGF-beta binding protein is capable of binding a first TGF-beta superfamily member that is a first cognate ligand; and

(b) the second TGF-beta binding protein is capable of binding a second TGF-beta superfamily member that is a second cognate ligand;

wherein the complex is incapable of binding to the first cognate ligand.

3. An isolated complex comprising a first and a second TGF-beta binding protein in specific association, wherein;

(a) the first TGF-beta binding protein is capable of binding a first TGF-beta superfamily member that is a first cognate ligand; and

(b) the second TGF-beta binding protein is capable of binding a second TGF-beta superfamily member that is a second cognate ligand;

wherein the complex is incapable of binding to either of the first and second cognate ligands.

4. The complex of claim 3 wherein the first TGF-beta binding protein comprises a sclerostin polypeptide and the first cognate ligand is at least one polypeptide selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6 and BMP-7, and wherein the second TGF-beta binding protein comprises a chordin polypeptide and the second cognate ligand is a polypeptide selected from the group consisting of BMP 2, BMP-4 and BMP-7.

5. The complex of claim 3 wherein the first TGF-beta binding protein comprises a sclerostin polypeptide and the first cognate ligand is a polypeptide selected from the group consisting of BMP-5 and BMP-6, and wherein the second TGF-beta binding protein comprises a noggin polypeptide and the second cognate ligand is a polypeptide selected from the group consisting of BMP-2, BMP-4, BMP-7, and GDF-5.

6. A method for identifying an agent that modulates binding between a TGF-beta binding protein and a BMP antagonist protein comprising the steps of:

(a) contacting, in the absence and presence of a candidate agent, a TGF-beta binding protein and a BMP antagonist protein under conditions and for a time sufficient to permit specific association of the TGF-beta binding protein and the BMP antagonist protein to form a complex according to claim 1; and

(b) determining a level of complex that is present, wherein a difference in the level of complexes in the presence of the candidate agent relative to

the level in the absence of the candidate agent indicates the agent modulates binding between the TGF-beta binding protein and the BMP antagonist protein

7. A method for identifying an agent that modulates binding between a first TGF-beta binding protein and a second TGF-beta binding protein comprising the steps of:

(a) contacting, in the absence and presence of a candidate agent, a first and a second TGF-beta binding protein under conditions and for a time sufficient to permit specific association of the first and second TGF-beta binding proteins to form a complex according to any one of claims 2-5; and

(b) determining a level of complex that is present, wherein a difference in the level of complexes in the presence of the candidate agent relative to the level in the absence of the candidate agent indicates the agent modulates binding between the first TGF-beta binding protein and the second TGF-beta binding protein.

8. The method of either claim 6 or 7 wherein the candidate agent decreases the specific association of proteins to form a complex.

9. The method of either claim 6 or 7 wherein the candidate agent increases the specific association of proteins to form a complex.

10. The method of either claim 6 or 7 wherein the candidate agent stabilizes the specific association of proteins to form a complex.

11. The method of either claim 6 or 7, wherein the candidate agent is selected from the group consisting of an organic molecule, a natural product, a peptide, an oligosaccharide, a nucleic acid, a lipid, an antibody or binding fragment thereof, and a cell.

12. The method of either claim 6 or 7, wherein the candidate agent is obtained from a library of compounds.

13. The method of claim 12, wherein the library is selected from the group consisting of a random peptide library, a natural products library, a combinatorial library, an oligosaccharide library and a phage display library.

14. An agent identified according to the method of either claim 6 or claim 7.

15. A method for modulating bone density comprising administering to a subject in need thereof an agent which modulates the interaction between (i) a sclerostin polypeptide that is capable of specifically binding a first TGF-beta superfamily member polypeptide that is selected from the group consisting of a BMP-5 polypeptide and a BMP-6 polypeptide, and (ii) a BMP antagonist protein that is selected from the group consisting of a Chordin polypeptide and a Noggin polypeptide, said BMP antagonist protein being capable of specifically binding at least one second TGF-beta superfamily member polypeptide that is selected from the group consisting of a BMP-2 polypeptide, a BMP-4 polypeptide and a BMP-7 polypeptide.

16. The method of claim 15 wherein the agent comprises a mimetic of the Chordin polypeptide or of the Noggin polypeptide.

17. The method of claim 15 wherein the agent modulates bone mineralization.